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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
10/009,660	12/07/2001	Joseph E. Martinez	6395-61708	1922

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EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	7

DATE MAILED: 04/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/009,660	MARTINEZ ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3-4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-23 are under consideration in the office action.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration for the date signing of George M. Carlone. See 37 CFR 1.52(c).

It does not identify the city and either state or foreign country of residence of inventor J.E. Martinez. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Drawings

3. The drawings were received on December 7, 2001.

Specification

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. The use of the trademark EDANS ™, BODIPYTM and similar reagents has been noted throughout the application on at least page 9. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 11 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 11 and 21 are drawn to a method wherein the detection of the functional antibody indicates the efficacy of the vaccine.

The instant specification fails to provide any data that show that detection of functional antibodies indicates the efficacy of the vaccine. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to an infection or disease induction. The vaccine art is highly unpredictable and the instant specification fails to provide any information that the detection of functional antibodies correlates to the efficacy of a vaccine. There are no immunological experiments

provided to demonstrate that the detection of functional antibodies correlates to the efficacy of the vaccine. There is merely a general outline that does not apply directly to the instant invention. It is unclear that one of skill in the art could follow these general guidelines and determine efficacy based on the detection of functional antibodies. The specification does not provide substantive evidence that vaccine efficacy is correlative to the detection of functional antibodies. This demonstration is required for the skilled artisan to be able to use the claimed method for their intended purpose of determining efficacy of the vaccine. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the method of detection and correlating the detection with vaccine efficacy.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies" (page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al., wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to use the method of detection without the prior demonstration of vaccine efficacy. Thus, the method could identify a functional antibody

that fails to elicit protective immunity, and thereby provide false evidence of vaccine efficacy.

The specification fails to adequately disclose a description of the claimed method with the ability to determine vaccine efficacy, thus a skilled artisan would be required to de novo locate, identify and characterize the method with the recited abilities. Accordingly, this would require undue experimentation given the fact that the specification is fails to teach such broadly claimed vaccine efficacy characteristics. Thus, the art indicates that it would require undue experimentation to use the claimed method without the prior demonstration of vaccine efficacy. Therefore the claims are rejected.

7. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of the claims is drawn to a method of simultaneously detecting and distinguishing a plurality of different functional antibodies, however the recited steps within the method comprise combining antigens, complement and effector cells; incubating the combination and detecting internalized antigens. There is no positively recited step that recites how to distinguish a plurality of functional antibodies. Therefore, the goal of the preamble is not commensurate with the steps of the method drawn to simultaneously detecting and distinguishing a plurality of different functional antibodies.

8. Claims 1, 13, 22 and 23 are unclear. The claims state combining sample containing antigens, complement and effector cells; however the claims fail to state what the sample is being combined with. Therefore clarification is requested to overcome the rejection.

9. Claim 2-3 recite the limitation "the first plurality of different fluorescent molecules" in the claims. There is insufficient antecedent basis for this limitation in the claims.

10. Claims 4-8 and 16-18 recite the phrase "a bacterial molecule derived from..." however it is unclear how to define "derived from". The specification does not teach how to make derivatives from a different serotype of a single bacterial species. The derivative language is vague and indefinite because the characteristics needed to determine whether an unknown could be considered a derivative of a bacterial species are unknown. The specification neither discloses a definition for derived from, nor does it teach a requisite amount of retained qualities needed or characteristics necessary to determine whether a molecule can be considered as derived from a different serotype of a single bacterial species. Therefore the claims are unclear.

11. Claim 10 is vague and indefinite. The claim refers to an individual has been immunized with a vaccine. However, there is no description or limitation to the kind of vaccine the individual is immunized with. The fact that the vaccine contains antigens is not sufficient to define the vaccine. Thus, clarification is requested.

12. The term "a standard hematology unit" in claim 22 is a relative term that renders the claim indefinite. The term "a standard hematology unit" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, the metes and bounds of the term cannot be ascertained and the claim is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-10, 12-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Romero-Steiner et al., in view of Sveum et al.

Romero-Steiner et al., teach the standardization of an opsonophagocytic assay for the measurement of functional antibody activity against *Streptococcus pneumoniae* using differentiated HL-60 cells. Opsonophagocytic assays for *Streptococcus pneumoniae* are traditionally used with peripheral blood leukocytes (PBLs) as effector cells and a variety of techniques such as radioisotopes, flow cytometry, microscopic and viability assays to measure opsonophagocytic activity (page 415). Studies with using differentiated HL-60 cells to measure complement-dependant opsonophagocytic activity in sera from individuals vaccinated with various pneumoccal vaccines have been

described in the prior art (page 415). Thus, HL-60 cells are an alternative to PBL effector cells for opsonophagocytosis of *S.pneumoniae* serogroups 4,6B, 9V, 14, 18C 19F and 23F (page 415). Table 1 teaches using different strains and serogroups of *S.pneumoniae* in the study. The HL-60 is the preferred effector cells since it expresses Fc receptors such as FcRI, FcRII and FcIII that bind antibody/antigen complexes and facilitate internalization. The receptor analysis shows the presence of such receptors as determined by flow cytometric analysis of the HL-60 cells and purified PBLs 9page 417). It has been determined that complement like opsonin, is necessary for the clearance of *pneumococci in vivo* (page 415). The authors also state that the measurement of functional antibody activity by opsonophagocytosis has not been correlated with protection, yet may be used as a surrogate of protection for the evaluation of pneumococcal vaccines (page 415). Serum samples from both pre- and post-vaccination human patients were tested (page 416). The opsonophagocytic assay combined the HL-60 effector cells in wells with serum sample and opsonophagocytosis buffer wherein following the incubation period, complement, being sterile baby rabbit serum, was kept frozen until use and was than added to the assay plate which was later incubated (page 416-417). Romero-Steiner et al., do not specifically recite internalization even though Romero-Steiner et al., make an implied reference to such.

Sveum et al., teach a two-color fluorescent method for the quantitative measurement of bacterial adherence and phagocytosis or ingestion of *Streptococcus pneumoniae* by human monocytes (abstract). The method employs a fluorescent naphthalimide, Lucifer Yellow VS that has been covalently linked to the bacterial cell

wall wherein bacteria were opsonized and allowed to adhere to monocytes (abstract). The ability of monocytes to ingest the bacteria was tested under a variety of conditions, using rabbit antibody to Lucifer Yellow (LY) derivatized with Texas Red (abstract). The LY was covalently linked onto groups on the pneumonococcal surface (page 258). Then an antibody directed against the LY molecule was employed that carried a second fluorescent color Texas Red (page 258). Monocytes with attached pneumoniae were incubated at various temperatures (page 259). Dual laser flow cytometry simultaneously quantitated the total number of monocyte associated *S.pneumoniae*, the method allows for separate analysis of the opsonins and receptors involved in bacterial adherence to phagocytes and in the ingestion process (abstract). The binding of *S. pneumoniae* showed the absolute requirement for serum opsonization (page 259). The prior art teaches that several control experiments were run along with the use of other labeling agents such as crystal violet, fluorescein, flurophores, trypan blue and acridine orange (page 263).

One having ordinary skill in the art would have been motivated to use beads as a labeling technique when such changes are merely alternative and functionally equivalent labeling systems. There is a reasonable expectation of success in using an equivalent bacterial antigen such as *Neisseria meningitidis*, since this has many useable serotypes and many attempt to vaccine against this bacterial infection. Likewise, an artisan would have had a reasonable expectation of success in switching the labeling pieces and using labeled beads when only the expected labeling effect would have been obtained when the prior art clearly teaches the detection of the label

and relating it to the presence of functional antibody. The use of alternative and functional equivalent labeling techniques would have been desirable to those of ordinary skill in the art based on the economics and availability of the components.

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the opsonophagocytic assay of Romero-Steiner et al., to incorporate the internalization aspect of the assay as taught by Sveum et al., because Sveum et al., teach that laser flow cytometry can simultaneously separately analysis ingestion or internalization of the antigen. One would have a reasonable expectation of success since Romero-Steiner et al., teach opsonophagocytic assays using the same claimed reagents such as the same antigen, complement and effector cells, having the same combination, incubation and detection steps and resulting in the same simultaneous detection and distinguishment of functional antibodies. Moreover, no more than routine skill would have been required to incorporate internalization steps into an already well-known assay that is capable of detecting and distinguishing functional antibodies based on the known ability of flow cytometry to distinguish functional antibodies.

Prior Art

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fischer (US Patent 5,571,511) teaches broadly reactive opsonic antibodies that react with staphylococcal antigens.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
March 18, 2003

LYNETTE R. F. SMITH
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